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EXAMINER	
GAMBEL, PHILLIP	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/501,102	CO ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *145,147 and 149-154* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *145,147 and 149-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed on 01/09/2008, has been entered.

Claims 145 and 154 have been amended.

Claims 1-143-144, 146, 148 and 155-160 have been canceled previously.

Claims 145, 147 and 149-154 are pending.

Again for the record as indicated previously, claims 145, 147 and 149-154, as they read on the elected invention, including the elected species of the combination of anti-B7-1 antibodies, anti-B7-2 antibodies and cyclosporin or rapamycin in the claimed methods are under consideration in the instant application.

Also, as noted previously, the previously amended recitation of administering an additional (third) agent, is read on administering cyclosporin or rapamycin as the additional (third) agent only.

Accordingly, the third agents other than cyclosporin or rapamycin are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 2(b) and M.P.E.P. 821.03.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 01/09/2008.

The rejections of record can be found in the previous Office Actions, mailed 04/10/2006, 11/06/2006 and 05/07/2007, 06/25/2007 and 10/09/2007.

3. Priority.
Applicant's arguments, filed 01/09/2008, and the examiner's position on the priority of the instant claims are essentially the same of record.

Currently, applicant's arguments rely upon the following.

The Examiner has objected to the introduction of the language "wherein an inhibitor of the CD40 or CD40 ligand costimulatory interaction is not administered to the transplant recipient." Specifically, the Examiner contends that neither the priority documents (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125; and U.S.S.N. 09/339,596, now U.S. Patent No. 6,913,747) nor the instant specification provide sufficient written description of the amended claim language. The Examiner further contends that "anti-CD40 antibodies were the only clear designation of a possible inhibitor of CD40:CD40 ligand interactions in the priority documents". With respect to the earliest priority document (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125), the Examiner alleges that the meaning of the term "α CD40 ligands" (column 18, lines 40-41) is unclear.

Applicants respectfully traverse, and maintain that the meaning of the term "α CD40 ligands" is clear and definite. The term " α CD40 ligands" refers to a ligand that binds to CD40, including anti-CD40 antibodies and soluble forms of CD40 ligand that block CD40 signaling. While the Examiner has noted that antibodies may be agonistic or antagonistic, Applicants point out that anti-CD40 antagonistic antibodies were known in the art at the time of filing. For example, Lederman et al. (U.S. Patent No. 5,474,771) discloses anti-CD40 antibody 5c8, which "inhibits T cell activation of B cells." Moreover, as the Examiner has noted, "monomericCD40L is considered antagonistic" (page 4, line 9 of the Office Action). In addition, a skilled artisan would readily recognize that administering a soluble form of a receptor would also antagonize signaling in a particular pathway. Evidence that the latter concept was known to a person of ordinary skill in the art at the time of filing may be found, for example, in Alegre, et al., Immunomodulation of transplant rejection using monoclonal antibodies and soluble receptors, Digestive Diseases and Sciences, 1995, 40:58-64 (emphasis added), which was cited in the Information Disclosure Statement filed February 3, 2003 and listed in the References Cited of the earliest priority document (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125). In view of the foregoing, Applicants submit that, given the knowledge available in the art at the time of filing, priority document U.S.S.N. 09/249,011 (now U.S. Patent No. 6,972,125) is enabling, at least, for the administration of anti-CD40 antibodies, soluble CD40 ligand, and CD40 receptor. Solely for the purpose of expediting prosecution and in no way conceding to the Examiner's rejections, Applicants have amended claims 145 and 154, rendering the Examiner's objection moot. Applicants therefore request reconsideration and withdrawal of the objection.

Here, again, applicant's arguments have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments have not been found persuasive for the reasons of record and again, reiterated herein for applicant's convenience.

The effective filing date of the instant claims is deemed as follows.

As addressed previously and reiterated / addressed herein for applicant's convenience,

It appears that applicant is relying upon limited species (e.g., "α CD40 ligands" in USSN 08/249,011 though it is not clear what "α CD40 ligands" was intended to mean, since this does not appear to be a designation of art; "anti-CD40 ligands" with anti-CD40 antibodies as the only designation of a possible inhibitor of CD40:CD40 ligand interactions clearly named in the priority documents).

Also as indicated previously and acknowledged by applicant in their latest rebuttal,

it was known at the time the invention was made, particularly as the time of the priority documents, that anti-CD40 antibodies were agonistic as well.

For example, with CD40L, monomeric CD40L is considered antagonistic, while multimeric CD40L is considered an agonistic.

While the Examples of the priority documents and herein do not necessarily employ "inhibitors of CD40 or CD40 ligand interactions" or currently amended to "an anti-CD40 antibody, soluble CD40 ligand or CD40 receptor",

clearly, the priority documents and the instant disclosure as well contemplate combination therapy (e.g. see the instant Summary of the Invention).

Further as indicated previously, it appears that applicant's arguments rely, in part, on disclosures not necessarily found in the instant specification, or the priority documents.

Rather than relying upon the limited disclosures of the priority documents, applicant is relying upon disclosures outside the written description of the priority documents (e.g., Lederman et al. U.S. Patent No. 5,474,771; Alegre et al. Digestive Diseases and Sciences 40: 58-64, 1995) to support "inhibitors of CD40 or CD40 ligand interactions" or currently amended to "an anti-CD40 antibody, soluble CD40 ligand or CD40 receptor".

While It appears that priority USSN 09/249,011, now U.S Patent No. 6,972,125, provides for the recitation of "α CD40 ligands" as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see column 18, paragraph 2 of U.S. Patent No. 6,972,125);

while it appears that priority USSN 09/339,596, filed 06/24/1999, now U.S. Patent No. 6,913,747, provides for the recitation of "anti-CD40 antibodies, and analogs thereof", as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see column 24, paragraph 5 of U.S. Patent No. 6,913,747);

these priority documents do not provide sufficient written description of the newly amended claim limitation "wherein an anti-CD40 antibody, soluble CD40 ligand or CD40 receptor" are not administered to the transplant recipient", as broadly claimed in the instant claims.

While it appears that the instant USSN 09/501,102 provides for the recitation of "anti-CD40 pathway inhibitors (e.g. anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway" as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see page 42, paragraph 2 of the instant specification);

again, the instant application does not provide sufficient written description of the newly amended claim limitation "wherein an inhibitor of CD40 or CD40 ligand costimulatory interaction is not administered to the transplant recipient", as broadly claimed in the instant claims.

Again, the instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Further, neither the priority applications nor the instant application have provides a sufficient description of a representative number of species of "inhibitors of CD40 or CD40 ligand" to represent the entire genus of "inhibitors of CD40 or CD40 ligand", broadly encompassed by the current claims.

Again as noted previously, it is not clear what "α CD40 ligands" was intended to mean, since this does not appear to be a designation of art.
Also, it appears that anti-CD40 antibodies were the only clear designation of a possible inhibitor of CD40:CD40 ligand interactions in the priority documents
Further, there was no discussion of agonistic and antagonistic properties of anti-CD40 antibodies nor of the CD40 ligand itself either in the priority documents or in the instant application as filed.

For example, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972). Also see MPEP 2163.05.

Again, it is maintained that applicant'sreliance upon the genus of "drugs" and the disclosure of certain "inhibitors of CD40 or CD40 ligand" (e.g. anti-CD40 antibodies, anti-CD40 ligand antibodies) does not provide sufficient written description for certain "inhibitors of CD40 or CD40 ligand", as currently claimed.

As indicated previously, there does not appear to be sufficient description showing *possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics*, sufficient to show the applicant was in possession of the genera of "α CD40 ligands" "anti-CD40 ligands" and "small molecule inhibitors of the CD40 pathway" consistent with written description provisions of 35 USC 112, first paragraph, and the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday January 2001.

Therefore, there appears to be insufficient written description for the phrase "wherein an inhibitor of CD40 or CD40 ligand costimulatory interaction is not administered to the transplant recipient", as broadly claimed in the instant claims in the priority documents as well as in the instant specification.

Therefore, given the lack of written description of the claimed methods as indicated herein and below, the instant claims do not appear to have the priority date of USSNs 09/339,596 and 09/249,011.

Also, as pointed out previously, applicant's amended claims, filed 09/25/2007, which included the recitation of the Markush of

"(third) agents selected from the group consisting of: calcineurin inhibitor, steroid, and immunosuppressive agent that arrest the growth of immune cells, methotrexate, transplant salvage pathway inhibitor, IL-2 receptor antagonist, and analogs thereof, and wherein an inhibitor of the CD40/ CD40 ligand costimulatory interaction is not administered to the transplant recipient"

are not readily apparent in applicant's priority documents USSNs 09/339,596 and 09/249,011, particularly the written description of

"calcineurin inhibitor", "immunosuppressive agent that arrest the growth of immune cells", "transplant salvage pathway inhibitor", "IL-2 receptor antagonist" and "analogs" in addition to "soluble CD40 ligand or CD40 receptor".

If applicant desires priority back to their priority documents,
applicant is invited to point out and provide documentary support for the priority of the instant claims

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Applciant's arguments and reliance upon external documents has not been found persuasive for providing sufficient written description for the claimed "(third) agents", including "soluble CD40 ligand or CD40 receptor" as well as "calcineurin inhibitor", "immunosuppressive agent that arrest the growth of immune cells", "transplant salvage pathway inhibitor", "IL-2 receptor antagonist" and "analogs" in applicant's priority documents USSNs 09/339,596 and 09/249,011.

4. Claims 145, 147 and 149-154 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:

"wherein an "a soluble CD40 ligand or CD40 receptor" is not administered to the transplant recipient".

Applicant's amendment, filed 01/092008, simply asserts that the claims have been amended thereby rendering the previous rejection moot.

Applicant's arguments, filed 01/09/2008d the examiner's rebuttal are essentially the same of record and addressed above in Section 3.

The recitation of wherein an "a soluble CD40 ligand or CD40 receptor" is not administered to the transplant recipient" is not readily apparent either in the pending or in the earlier priority applications.

While It appears that priority USSN 09/249,011, now U.S Patent No. 6,972,125, provides for the recitation of "α CD40 ligands" as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see column 18, paragraph 2 of U.S. Patent No. 6,972,125);

while it appears that priority USSN 09/339,596, filed 06/24/1999, now U.S. Patent No. 6,913,747, provides for the recitation of "anti-CD40 antibodies, and analogs thereof", as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see column 24, paragraph 5 of U.S. Patent No. 6,913,747);

these priority documents do not provide sufficient written description of the newly amended claim limitation "wherein an anti-CD40 antibody, soluble CD40 ligand or CD40 receptor" are not administered to the transplant recipient", as broadly claimed in the instant claims.

While it appears that the instant USSN 09/501,102 provides for the recitation of "anti-CD40 pathway inhibitors (e.g. anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway" as another drug that can be administered with B7-1- / B7-2-specific antibodies" (e.g., see page 42, paragraph 2 of the instant specification);

again, the instant application does not provide sufficient written description of the newly amended claim limitation "wherein an "a soluble CD40 ligand or CD40 receptor" is not administered to the transplant recipient", as broadly claimed in the instant claims.

Again, the instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Further, neither the priority applications nor the instant application have provides a sufficient written description of a representative "a soluble CD40 ligand or CD40 receptor", currently encompassed by the current claims.

Again as noted previously, it is not clear what "α CD40 ligands" was intended to mean, since this does not appear to be a designation of art.

Also, it appears that anti-CD40 or anti-CD40L antibodies were the only clear inhibitors described in the priority documents

Further, there was no discussion of agonistic and antagonistic properties of anti-CD40 antibodies nor of the CD40 ligand itself either in the priority documents or in the instant application as filed.

For example, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972). Also see MPEP 2163.05.

Again, it is maintained that applicant's reliance upon the genus of "drugs" and the disclosure of certain "inhibitors of CD40 or CD40 ligand" (e.g. anti-CD40 antibodies, anti-CD40 ligand antibodies) does not provide sufficient written description for distinct inhibitors of CD40 or CD40 ligand, namely "a soluble CD40 ligand or CD40 receptor", as currently claimed.

As indicated previously, there does not appear to be sufficient description showing *possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics*, sufficient to show the applicant was in possession of the genera of "α CD40 ligands" "anti-CD40 ligands" and "small molecule inhibitors of the CD40 pathway" consistent with written description provisions of 35 USC 112, first paragraph, and the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday January 2001.

Therefore, there appears to be insufficient written description for the phrase "wherein an "a soluble CD40 ligand or CD40 receptor" is not administered to the transplant recipient" is not administered to the transplant recipient", as broadly claimed in the instant claims in the priority documents as well as in the instant specification.

Therefore, given the lack of written description of the claimed methods as indicated herein and below, the instant claims do not appear to have the priority date of USSNs 09/339,596 and 09/249,011.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Further, neither the priority applications nor the instant application have provides a sufficient description of the species of "a soluble CD40 ligand or CD40 receptor" recited by the current claims.

Given the lack of sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "α CD40 ligands" "anti-CD40 ligands" and "small molecule inhibitors of the CD40 pathway",
applicant's newly added limitation of reciting a negative limitation based upon the limited disclosure in the instant and priority applications raised new matter under 35 USC 112, first paragraph, written description.

Therefore, there appears to be insufficient written description for the phrase "wherein an "a soluble CD40 ligand or CD40 receptor" is not administered to the transplant recipient", as claimed in the instant claims in the priority documents as well as in the instant specification.

The specification as filed does not provide a sufficient written description or set forth the metes and bounds of this phrase. The specification does not provide blaze marks nor direction for the instant methods encompassing the above-mentioned "limitation", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above.
See MPEP 714.02 and 2163.06

Applicant's arguments of record and the examiner's rebuttal are essentially the same of record and addressed herein and above in Section 3.

Applicant's arguments have not been found persuasive.

5. Claims 145, 147 and 154 stand rejected under 35 U.S.C § 102(e) as being anticipated by Freeman et al. (U.S. Patent No. 6,605,279) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 01/09/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicants respectfully traverse the rejection. As the Examiner has admitted, "Freeman *et al.* differs from the claimed methods by not disclosing the well known use of immunosuppressives such as rapamycin and effective therapeutic antibody dosages in transplantation therapeutic regimens at the time the invention was made" (page 12, paragraph 10 of the Office Action). Therefore, Freeman *et al.* does not teach or suggest each and every element of the claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Although the reference is silent about the term "effective amounts", it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference.

Again, applicant is reminded that the instant claims are read on the elected invention, including the elected species of the combination of anti-B7-1 antibodies, anti-B7-2 antibodies and cyclosporin or rapamycin in the claimed methods are under consideration in the instant application.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

Freeman et al. teach methods of downregulating or suppressing T cell mediated immune responses, including the use of B7-1-specific and B7-2-specific antibodies in conjunction with other immunomodulating reagents such as cyclosporine or FK506, including it usefulness in situations of tissue and organ transplantation as well as GVHD (see entire document, particularly Other Therapeutic Reagents on columns 32-34).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

6. Claims 145, 147 and 149-154 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman et al. (U.S. Patent No. 6,605,279) in view of the well known use of immunosuppressives such as cyclosporin, FK506 and rapamycin and effective therapeutic antibody dosages in transplantation therapeutic regimens at the time the invention was made, as taught by de Boer et al. (U.S. Patent No. 5,757,034) (1449) essentially for the reasons of record.

Applicant's arguments, filed 01/09/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

De Boer *et al.* teaches away from the combination of anti-B7-1 and anti-B7-2 antibodies disclosed in Freeman *et al.* In doing so, de Boer *et al.* discloses "co-administration of a molecule that specifically binds to the B7-1 molecule but not to B7-2 or B7-3 and an immunosuppressive agent" (column 6, lines 37-39; emphasis added). Moreover, Example 14 in de Boer *et al.* is substantially dedicated to demonstrating the advantages of blocking only B7-1 signaling, in contrast to the blockage of B7-1 and B7-2 signaling in the instant claims. Indeed, in discussing the advantages of the disclosed B7-24 monoclonal antibody, de Boer *et al.* states that "signaling by B7-2 interaction with T cells is needed for tolerance" and "[w]ith the B7-24 antibody, this is not a problem because...it does not block B7-2" (column 28, lines 11-15; emphasis added). Finally, de Boer *et al.* states that "blocking both B7-1 and B7-2 does not result in alloantigen specific tolerance" (column 32, lines 51-52). These disclosures not only teach away from the combination of anti-B7-1 and anti-B7-2 antibodies disclosed in Freeman *et al.,* but the latter statement is in direct contrast to the Applicants' results, showing that treatment with antibodies to B7-1 and B7-2 prolongs survival in comparison to treatment with either antibody alone (see Example 23, pages 104-108, and Figure 28 of the specification). Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Contrary to appellant's argument that the references teaches away from the claimed invention, it is noted that a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the appellant." See In re Haruna, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001) and In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Also, in contrast to applicant's assertions; disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi USPQ 423 (CCPA 1971). A known or obvious composition does not patentable simply because it has been described as somewhat inferior to some other product for the same use. See In re Gurley 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See MPEP 2123.

General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc. , 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

The prior art references must be considered in their entirety.

Here in contrast to applicant's assertions of teaching away by the prior art because the references indicate a successful method of treating transplant patients or inhibiting transplant rejection by targeting both B7-1 and B7-2 as well as other immunosuppressive agents, such as cyclosporine and rapamycin (e.g., see the teachings of Freeman et al. of record and reiterated below).
Also, note that De Boer et al. teach the use of B7-specific antibodies in combination with immunosuppressive agents such as cyclosporin, FK506 and rapamycin (e.g., see column 14, paragraphs 2-3) in therapeutic amounts and modes of administration encompassed by the claimed invention (e.g., see column 16, paragraph 5) (see entire document).

In contrast to applicant's assertions, there is no discouragement nor skepticism in the prior art for providing combination therapy in transplantation therapeutic regimens, including providing both anti-B7-1 and anti-B7-2 antibodies as well as various immunosuppressives, including cyclosporin and rapamycin at the time the invention was made.

That the experimental results of De Boer et al. would suggest the lack of the use of anti-B7-2 antibodies for achieving tolerance does not take away from the clear teachings of the primary reference Freeman et al. in combining antagonists of both anti-B7-1 and anti-B7-2 antibodies in transplantation therapeutic regimens at the time the invention was made.

Further, applicant is reminded that the instant claims are read on the elected invention, including the elected species of the combination of anti-B7-1 antibodies, anti-B7-2 antibodies and cyclosporin or rapamycin in the claimed methods are under consideration in the instant application.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

Freeman et al. teach methods of downregulating or suppressing T cell mediated immune responses, including the use of B7-1-specific and B7-2-specific antibodies in conjunction with other immunomodulating reagents such as cyclosporine or FK506, including it usefulness in situations of tissue and organ transplantation as well as GVHD (see entire document, particularly Other Therapeutic Reagents on columns 32-34).

While Freeman et al. teach the administration of therapeutically effective amounts of the therapeutic compositions, wherein amounts of effective dosages are administered for periods of time necessary to achieve the desired results (e.g. see Administration of Therapeutic Forms of B Lymphocytes Antigens on columns 37-39), Freeman et al. differs from the claimed methods by not disclosing the well known use of immunosuppressives such as rapamycin and effective therapeutic antibody dosages in transplantation therapeutic regimens at the time the invention was made .

De Boer et al. teach the use of B7-specific antibodies in combination with immunosuppressive agents such as cyclosporin, FK506 and rapamycin (e.g., see column 14, paragraphs 2-3) in therapeutic amounts and modes of administration encompassed by the claimed invention (e.g., see column 16, paragraph 5) (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the teachings of Freeman et al. to incorporate the well known use of immunosuppressives such as as cyclosporin, FK506 and rapamycin and effective therapeutic antibody dosages in transplantation therapeutic regimens at the time the invention was made to achieve the desired therapeutic result of inhibiting graft rejection and promoting long term graft survival with effective amounts of standard immunosuppressives and effective amounts of therapeutic antibodies. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Also, as to the use of a combination of immunosuppressive therapy in transplantations therapeutic regimens,
methods of administration are a result effective variable.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

7. No claim allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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